Practice of Epidemiology

Importance of Routine Public Health Influenza Surveillance: Detection of an Unusual W-Shaped Influenza Morbidity Curve

Peter Georgantopoulos, Eleanor Peters Bergquist, Richard C. Knaup, John R. Anthony, Thomas C. Bailey, Michael P. Williams*, and Steven J. Lawrence

* Correspondence to Dr. Michael P. Williams, Communicable Disease Control Services, St. Louis County Department of Health, 111 South Meramec Avenue, Clayton, MO 63105 (e-mail: mwilliams@stlouisco.com).

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Seasonal influenza causes excess morbidity and mortality at the extremes of age: It disproportionately affects the very young and the very old, typically resulting in "U"-shaped age-distributed curves. By means of a well-established public health department surveillance system using positive influenza tests submitted from sentinel sites, the authors generated annual influenza-specific morbidity curves over a 10-year period (1998–2008) for St. Louis County, Missouri. The authors detected an unusually high incidence of cases of medically attended test-positive influenza, particularly in young adults, during the 2007–2008 season, resulting in an unexpected "W"-shaped age-distributed morbidity curve that was distinctly unique in comparison with the prior 9 influenza seasons. Public health influenza surveillance programs are useful tools for detecting emerging epidemiologic trends that may have clinical importance.

age groups; influenza, human; population surveillance; public health

Seasonal influenza incidence varies with each annual influenza epidemic; however, it is commonly believed that children and adolescents are the primary reservoir, and they have the highest age-group-specific incidence rates (1–3). Typically, seasonal influenza produces a "U"-shaped mortality distribution across age groups, disproportionately affecting young children and the elderly. Deviations from the "U"-shaped curve were observed during 20th-century influenza pandemics, most notably in 1918–1919, when increased mortality in young adults resulted in a distinctive "W"-shaped age-distributed mortality curve (1, 4). Hypothetical explanations for the central peak in the "W" include evocation of an overly exuberant immune response in young adults, higher rates of bacterial pneumonia in this age group, and the possibility of a lack of prior exposure to an immunologically similar virus that transiently circulated more than 30 years prior to the pandemic (4–6).

Community influenza surveillance is a key tool for defining the beginning and end of influenza season, estimating the burden of disease in the community, and identifying unusual epidemiologic trends (7). Factors that influence influenza surveillance vary between jurisdictions, between levels of government, and across time within jurisdictions (7). Considerations include the laboratory or clinical case definition used, the number of participating reporting sites, the diversity of participating reporting sites, and the reporting system. Estimates of actual influenza-attributable disease burden have been difficult to obtain historically; thus, surrogate markers have more commonly been used. "Influenza-like illness," which is a defined syndrome often associated with influenza, has been used as a surrogate for influenza morbidity in both health-care and public health settings. However, this approach lacks specificity for influenza, because other illnesses present similarly (3). It also lacks sensitivity, particularly in young children, the elderly, and hospitalized patients, in whom influenza may present atypically (3, 8). Another example of a surrogate measure is the proportion of deaths due to the combined broad diagnoses of
pneumonia and influenza; however, this also lacks specificity for influenza (3). While the relatively nonspecific surrogate markers may be useful in defining the boundaries of the influenza season and may produce a relative estimate of disease burden, more specific surveillance measures allow for detection of unusual epidemiologic trends attributable to influenza itself that may generate new hypotheses regarding the clinical impact of this virus.

The St. Louis County Department of Health (St. Louis County, Missouri) has been collecting data on cases of medically attended test-positive influenza (MATPI) in a consistent manner for the last 10 influenza seasons, through a well-established surveillance system that allows for detection of unique trends that may lie outside the norm of prior seasons. Using this surveillance system, we identified a distinctive “W”-shaped morbidity distribution during the 2007–2008 influenza season.

MATERIALS AND METHODS

Surveillance system

St. Louis County, Missouri, is a suburban community of approximately 1 million people. Since the 1998–1999 influenza season, the St. Louis County Department of Health has annually collected data on MATPI from up to 21 distinct sites. These sites include all 10 hospitals located in St. Louis County, 9 outpatient clinics, 1 university health center, and a reference laboratory. Fifteen of these 21 sources participated in each of the seasons during the 10-year study period. These 15 sites collectively accounted for 77.5%–99.6% of the cases reported in each of the last 10 seasons.

This local public-health-based surveillance system captures data on age and influenza type for each case. MATPI cases are classified as type A, type B, or unknown (influenza-positive but not typed). MATPI cases are defined by means of a positive viral culture, direct fluorescent antibody test, or rapid antigen test performed on respiratory specimens obtained from patients who visited a physician’s office, emergency department, or hospital. The specific ages of cases are available for every season except 2004–2005 and 2005–2006, when ages were reported in aggregate form only, in the following Missouri Health Surveillance Information System (MOHSIS) groups: <2, 2–4, 5–14, 15–24, 25–49, 50–64, and ≥65 years. For purposes of receiving consistent data, the state of Missouri requires all local health departments to report the numbers of influenza cases in their respective jurisdictions aggregated into these age groups. Data on the number of tests performed and the number of visits to each sentinel site are not reported and are not available.

Age distribution comparison

Three age group distributions were used for comparison purposes. The first was the Centers for Disease Control and Prevention (CDC) age distribution for laboratory-confirmed influenza cases and consisted of the following age groups: <1, 1–4, 5–24, 25–44, 45–64, and ≥65 years. The second was the MOHSIS age groups for laboratory-confirmed influenza cases (see above). The third age distribution used was 5-year age groups. The 2004–2005 and 2005–2006 influenza seasons were excluded from the CDC and 5-year age groups because only MOHSIS aggregated numbers were available.

We determined MATPI rates using the number of influenza-positive cases per 1,000 population, based on the 2005 local census estimates for St. Louis County (Division of Research and Statistics, St. Louis County Department of Planning, unpublished data). The 2005 census estimates for St. Louis County were used instead of the 2000 US Census estimates because 1) they were closer to the midpoint of the 10 influenza seasons that were compared and 2) they were the most updated census data available for St. Louis County (the overall difference between the 2005 county census estimates and the 2000 US Census estimates for St. Louis County was 0.36%). The 2005 census estimates for St. Louis County showed a population of 1,012,636 persons, 47.4% of whom were male. The CDC age group 5–24 years comprised 275,205 persons (27.2% of the entire population), the MOHSIS age group 15–24 years comprised 128,206 persons (12.7%), and the 5-year age group 20–24 years comprised 57,564 persons (5.7%). We estimated overall surveillance-based MATPI rates for each season by dividing all of the MATPI cases (in aggregate and by influenza type) for that specific season by the total 2005 St. Louis County census estimate; rates were expressed per 1,000 total population. We estimated age-stratified MATPI rates by dividing the number of MATPI cases within each age group by the population census estimate within that age group; these rates were also expressed per 1,000 population.

We conducted a run control test for the total number of influenza cases for each influenza season to determine whether any particular season differed from the others in terms of number of influenza cases. The run control test used the mean number of influenza cases for all 10 seasons, and 2 standard deviations from that mean was used as the cutoff (9). We also used the run control test to compare the seasonal incidence of MATPI type A with the age-group-specific incidence of MATPI type A for each of the influenza seasons using the 3 different age distributions. Any season group with a difference between its group MATPI type A incidence rate and the season’s MATPI type A incidence rate that was greater than or less than 2 standard deviations from the mean difference between group MATPI type A incidence rates and seasonal MATPI type A incidence rates was determined to be statistically significant. We created trend lines for seasonal MATPI incidence rates collectively and by influenza type for the 3 age group distributions. We used analysis of variance to determine whether rates within specific groups differed between influenza seasons for all age group distributions, and to compare rates between groups within the 2007–2008 influenza season for all age group distributions. We conducted Tukey’s honestly significant difference test for any significant results to determine the locations of differences in rates between groups and between seasons. We were able to link MATPI cases to reporter sites for the 2006–2007 and 2007–2008 seasons only, and we conducted 2-way fixed-effects analysis of variance to determine whether there was a difference in MATPI incidence rates after controlling for type of reporting site (hospital vs. nonhospital) and season, by age group.
In all statistical analyses, we used a 2-tailed \( P \) value of <0.05 for statistical significance. All data management and statistical analyses were performed in SPSS, version 17 (SPSS, Inc., Chicago, Illinois).

RESULTS

MATPI surveillance incidence rates

The national, Missouri, and St. Louis County influenza surveillance programs showed that the 2007–2008 influenza season was remarkable in terms of MATPI incidence in comparison with previous seasons (Table 1). The overall MATPI incidence in St. Louis County for the 2007–2008 influenza season was 3.51 cases per 1,000 population. Within St. Louis County, the previous 9 influenza seasons (1999–2007) had a mean overall MATPI incidence of 0.99 cases per 1,000 population, with a low of 0.26 cases per 1,000 persons in the 2000–2001 influenza season and a high of 1.84 cases per 1,000 persons in the 2005–2006 influenza season. The 3,550 reported cases in St. Louis County were significantly greater than any of the totals for the previous 9 seasons (run control test, \( P < 0.001 \)). Two reporting sources, both urgent care centers, were added in 2007–2008. These 2 new sources accounted for 28 (0.8%) of the 3,550 influenza cases reported in 2007–2008, with 4 (14.3%) of the 28 cases occurring in the age group 20–24 years. The 2007–2008 season also remained significantly different (run control test, \( P < 0.05 \)) from the previous influenza seasons, even after removal of the 28 cases from the 2 additional sites added for the season. The majority of cases for the 2007–2008 influenza season were caused by influenza type A (79.3% of typed isolates) and were reported from hospitals (69.5%).

W-shaped morbidity curve and effect of age groups

An influenza morbidity curve using the MOHSIS and CDC age group distributions (Figure 1, panels A and B) revealed an apparent central peak in influenza incidence within the adolescent/young adult age groups, with the peak becoming more evident with the MOHSIS age distribution than with the CDC age distribution. There was a distinct central peak that was located in the age group 15–24 years for the MOHSIS age distribution (438 MATPI type A cases). These cases were located in the broader CDC age group 5–24 years (727 MATPI type A cases). The morbidity curve shifted into a more pronounced and refined “W” shape when MATPI incidence was stratified into the narrower 5-year age groups (Figure 1, panel C). The central peak for the 5-year age groups was located in the age range 20–24 years (727 MATPI type A cases). Not only did the central peak become more prominent using the 5-year age distribution, it also became evident that MATPI incidence for older persons (those aged ≥65 years) continued to increase with increasing age even after age 65 years, which is the upper-end limit used for both the CDC and MOHSIS age distributions. The age range 20–24 years for the 5-year age groups during the 2007–2008 influenza season had 4.4 times the number of MATPI cases as the aggregate seasonal mean number of MATPI cases for the 8 evaluable seasons, 1998–2004 and 2006–2008 (Table 2).
The differences between the seasonal MATPI type A incidence rates and the 19- to 24-year age-group-specific MATPI type A incidence rates (MOHSIS age distribution, $P < 0.05$), as well as the 20- to 24-year age-group-specific MATPI type A incidence rates (5-year age distribution, $P < 0.001$), were statistically significant during the 2007–2008 influenza season only (Figure 2, panels A and D). However, the differences between the seasonal MATPI type A incidence rate and the 5- to 24-year age-group-specific MATPI type A incidence rate (CDC age distribution), as well as the 15- to 19-year age-group-specific MATPI type A incidence rate (5-year age distribution), were not statistically significant ($P > 0.05$) for any influenza season (Figure 2, panels B and C).

**Effect of influenza type**

Five-year age stratification by influenza type revealed that the central peak in the age group 20–24 years was primarily due to influenza type A (Figure 3). Analysis of variance, followed by Tukey’s honestly significant difference test, confirmed that the 2007–2008 influenza A incidence rate was higher than the rates in previous years at the central peak for both the MOHSIS age distribution (age group 15–24 years; $F = 73.36, P ≤ 0.001$) and the 5-year age distribution (age group 20–24 years, excluding the 2004–2005 and 2005–2006 seasons; $F = 93.56, P ≤ 0.001$). Incidences for influenza B in the same age groups were not different in 2007–2008 than in prior seasons (age group 20–24 years, excluding the 2004–2005 and 2005–2006 seasons; $F = 1.922, P = 0.268$). The 2007–2008 influenza A MATPI incidence within the age group 20–24 years remained significantly higher than incidence in the 2006–2007 season after adjustment for data source (hospital vs. nonhospital) by 2-way fixed-effects analysis of variance ($P < 0.001$). The influenza A MATPI incidence for the age group 20–24 years in the 2007–2008 influenza season also remained significantly higher after adjustment for data source in comparison with the age groups 15–19 years ($P = 0.012$) and 25–29 years ($P = 0.018$) within the 2007–2008 season.

**DISCUSSION**

The 2007–2008 influenza season in St. Louis County, Missouri, was notable for an overall increase in surveillance-based incidence rates of MATPI cases and a “W”-shaped age-distributed morbidity curve. The higher local MATPI incidence rate is not surprising given the national epidemiologic data confirming an unusually active influenza season in 2007–2008, which was probably due in large part to vaccine mismatch for the influenza A/H3N2 subtype and influenza B.

**Table 2.** Distribution of Cases of Medically Attended Test-Positive Influenza Type A by 5-Year Age Group and Influenza Season, St. Louis County, Missouri, 1998–2008

<table>
<thead>
<tr>
<th>Age Group, years</th>
<th>Influenza Season</th>
<th>Mean No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>29 11.15</td>
<td>55 20.23</td>
</tr>
<tr>
<td>5–9</td>
<td>5 1.92</td>
<td>37 14.12</td>
</tr>
<tr>
<td>10–14</td>
<td>12 4.62</td>
<td>28 10.69</td>
</tr>
<tr>
<td>15–19</td>
<td>18 6.92</td>
<td>27 10.31</td>
</tr>
<tr>
<td>20–24</td>
<td>21 8.08</td>
<td>16 6.11</td>
</tr>
<tr>
<td>30–34</td>
<td>5 1.92</td>
<td>6 2.29</td>
</tr>
<tr>
<td>35–39</td>
<td>16 6.15</td>
<td>12 4.58</td>
</tr>
<tr>
<td>40–44</td>
<td>14 5.38</td>
<td>13 4.96</td>
</tr>
<tr>
<td>45–49</td>
<td>12 4.62</td>
<td>6 2.29</td>
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<tr>
<td>50–54</td>
<td>4 1.54</td>
<td>45 4.23</td>
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<tr>
<td>55–59</td>
<td>16 6.15</td>
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</tr>
<tr>
<td>60–64</td>
<td>8 3.08</td>
<td>40 3.73</td>
</tr>
<tr>
<td>65–69</td>
<td>12 0.05</td>
<td>48 4.01</td>
</tr>
<tr>
<td>70–74</td>
<td>14 0.05</td>
<td>56 0.05</td>
</tr>
<tr>
<td>75–79</td>
<td>22 0.08</td>
<td>66 0.06</td>
</tr>
<tr>
<td>80–84</td>
<td>17 0.07</td>
<td>65 0.06</td>
</tr>
<tr>
<td>85–89</td>
<td>10 0.04</td>
<td>58 0.05</td>
</tr>
<tr>
<td>≥90</td>
<td>9 0.03</td>
<td>28 0.03</td>
</tr>
<tr>
<td>Total</td>
<td>260 100</td>
<td>1,072 100</td>
</tr>
</tbody>
</table>

*Age-specific data for cases occurring in the 2004–2005 and 2005–2006 influenza seasons were not available; therefore, 5-year age group distributions could not be determined for those influenza seasons.*
The increased activity was seen in nearly every age group and was mostly driven by influenza A. Surveillance-derived MATPI is a useful measure of morbidity for public health officials to use in estimating the influenza-attributable disease burden in the community. It is more specific than “influenza-like illness” because it requires laboratory evidence of the virus’ presence. Even in healthy adults, influenza-like illness has a positive predictive value of only 79%–88%, and this decreases dramatically in higher-risk populations such as the very young and the elderly (3).

Although excess morbidity, in the form of increased MATPI incidence, was seen in nearly every age group, there was a marked and significant peak of influenza A activity among young adults aged 20–24 years. The resulting “W”-shaped curve was distinctly different from the more typical “U”-shaped curves noted during the prior 9 years of surveillance (Figures 1 and 3), as determined using multiple statistical procedures (analysis of variance and run control tests). This unusual “W”-shaped age distribution in morbidity is reminiscent of the shape of the mortality curve during the 1918–1919 influenza A/H1N1 pandemic, when atypically high mortality in young adults was noted (1, 4).

The etiology of this observed phenomenon is unclear. To our knowledge, there were no substantive changes in

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**Figure 2.** Differences between seasonal overall and age-group-specific incidence rates of medically attended test-positive influenza (MATPI) for: A) the Missouri Health Surveillance Information System age group 15–24 years (1998–2008 influenza seasons); B) the Centers for Disease Control and Prevention age group 5–24 years (1998–2004 and 2006–2008 influenza seasons); C) the age group 15–19 years (1998–2004 and 2006–2008 influenza seasons); and D) the age group 20–24 years (1998–2004 and 2006–2008 influenza seasons). The solid line shows the mean difference (number of influenza-positive cases per 1,000 population) between the MATPI age group rate and the seasonal overall MATPI rate. The dashed lines show 2 standard deviations from the mean.
health-care-seeking behavior by young adults or changes in age-specific testing patterns by health-care providers in St. Louis County to account for this. Vaccine mismatch during the 2007–2008 influenza season was a factor in the overall increase in MATPI incidence; however, it probably would not explain the middle peak in young adults, because this age group historically has had very low vaccine uptake. Could the "W"-shaped curve result from host or virus factors hypothesized to be the cause of the 1918–1919 "W"-shaped mortality curve? Further clinical and virologic studies are necessary to determine whether the 2007–2008 influenza A isolates either exhibited enhanced virulence in young adults or were antigenically similar to a strain that circulated approximately 25–30 years prior.

In addition to the central peak of influenza A in young adults, there was also higher activity in 2007–2008 among older persons. Analysis of the data in the narrower 5-year age group distribution confirmed a continued linear increase in incidence with increasing age beyond the MOHSIS/CDC cutoff of 65 years. This trend was also seen in the 1999–2000 and 2003–2004 seasons. These data suggest that there is excess influenza risk in the oldest patients during more severe influenza seasons. More aggressive influenza prevention measures, including increasing vaccine uptake, are needed in this vulnerable population.

Our study had several important limitations. First, we were missing age-specific data for 2 of the influenza seasons in the surveillance period. However, visual and statistical analysis of the MOHSIS age groups strongly supports the conclusion that age distributions during the 2004–2005 and 2005–2006 seasons were similar to those of the prior 6 seasons. This underscores the importance of collecting age-specific data for MATPI surveillance, to allow for flexibility in defining age groups and to allow more detailed statistical analyses. Second, the described surveillance system was designed for use by the St. Louis County...
Department of Health and is not intended for strict clinical epidemiologic research. As such, it is flexible because it accepts MATPI data from any source that meets its criteria. The limitations of using this public health surveillance system include the fact that the number of reporting sites was not constant over the entire study period. However, most of the reporting sources remained constant, and the vast majority of MATPI cases were reported from these core sites. Third, data on the number of influenza tests conducted by each facility were not collected, because the goal was only to identify influenza-positive cases. Thus, it was impossible to estimate the proportions of performed tests that were positive. It is possible that influenza diagnostic tests were performed more frequently during the 2007–2008 influenza season than in prior years, leading to a higher proportion of detected cases. However, there is no reason to believe that changes in testing practices, if they occurred, would be limited to patients in the age group 20–24 years.

Fourth, data on the types of influenza tests that were conducted at each facility over the entire study period were not available. Differences in the sensitivities and positive predictive values of the various influenza diagnostic tests used could have resulted in site-to-site or year-to-year variation in MATPI incidence. However, they would not be expected to account for variation by age group. Fifth, data on the number of patients seen at each site were not collected because of the complexity of collecting that information over a broad range of different types of reporting sites. Sixth, data on multiple tests per case could not be collected, because the information reported from the participating sites is deidentified. However, any resulting overestimation of MATPI rates would not be expected to be confined to a single age group.

Finally, our ability to draw detailed conclusions is limited by a lack of information on clinical outcomes, mortality, subtyping, and virologic data, which could not be linked to the deidentified cases. In particular, there are currently no data on the rate of pneumonia and influenza mortality in St. Louis County during the 2007–2008 influenza season, which prevents our making any comparisons with the MATPI incidence rates of the St. Louis County influenza surveillance program, as well as any historical influenza mortality distributions.

These inherent limitations of public health surveillance data are outweighed by the ease with which the reporting sites can provide key information on MATPI cases, such as age, reporting week, and sex, in an easy-to-collect and timely manner. This allows the St. Louis County Department of Health to quickly disseminate broad statistics on influenza epidemiology within St. Louis County to healthcare professionals on a regular and timely basis during the course of the influenza season.

In summary, St. Louis County, Missouri, experienced an unusually severe influenza epidemic in 2007–2008, which was associated with an overall increase in numbers of influenza cases across age groups and an atypically high mortality in young adults, reminiscent of the 1918–1919 pandemic mortality distribution curve. Identification of this distribution was made possible through a well-established and well-maintained local surveillance system, along with the collection of age-specific (rather than categorized) age group data. The uniqueness of surveillance data on the 2007–2008 influenza season underscores 1) the need for public health departments to gather age-specific data and 2) the importance of public reporting by health departments as an initial step for further investigation into unique epidemiologic trends.

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Author affiliations: St. Louis County Department of Health, St. Louis, Missouri (Peter Georgantopoulos, Eleanor Peters Bergquist, Richard C. Knaup, John R. Anthony, Michael P. Williams); Department of Medicine, Division of Infectious Diseases, Washington University School of Medicine, St. Louis, Missouri (Thomas C. Bailey, Steven J. Lawrence); and Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research, St. Louis, Missouri (Steven J. Lawrence).

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